Chapter 12
Liver Transplantation

A1. Develop further refinements in the MELD and PELD systems that optimize allocation of livers for transplantation. The MELD and PELD systems are under continuing assessment by the Scientific Registry of Transplant Recipients (SRTR) and the NIH-funded registry entitled Studies of Pediatric Liver Transplantation (SPLIT). The inclusion of outcome or "transplant benefit" in allocation is being studied in depth. Attempts are being made to reduce geographic variation in allocation (Rodriguea-Luna H. *Amer J Transplant* 2005;5:2244). In adults, addition of serum sodium to the MELD score may improve accuracy (Biggins SW. *Hepatology* 2005;41:32). (20%)

A2. Identify biomarkers for acute cellular rejection and adequacy of immune suppression. Identification and diagnosis of early rejection remains a clinical challenge and often requires liver biopsy. The NIH encourages this area of research through the Immune Tolerance Network and the program announcement on "Development of Disease Biomarkers" (PA-05-098), which specifically mentions non-invasive means of detection of acute rejection, immune suppression and tolerance. (0%)

A3. Elucidate pathways of liver regeneration and identify targets for drug or cytokine/anticytokine therapy. Liver regeneration is an area of active support in multiple investigator-initiated studies. Underpinning the process of liver regeneration is an immense network of up- and down-regulated cellular signaling pathways. Studies have largely been in murine models (White P. *J Biol Chem* 2005; 280:3715). (10%)

B1a. Define efficacy of peginterferon and ribavirin in pre- and post-transplant HCV infection. A single center experience with peginterferon and ribavirin suggests that some patients with advanced hepatitis C can clear virus before transplantation and not suffer recurrence in the graft (Everson GT. *Hepatology* 2005; 42:255). The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) has initiated a controlled trial of peginterferon and ribavirin versus no treatment in patients with hepatitis C awaiting transplantation. (20%)

B1b. Improve safety and define role of living donor liver transplantation. The A2ALL cohort study has documented that living donor liver transplantation can improve patient outcome, but only after a steep learning curve in the first 20 patients (Olthoff KM. *Ann Surg* 2005;242:314). Further assessment, including long-term follow up of donors and recipients, is critical. (20%)

B2a. Delineate molecular pathways of immune tolerance to allografts in humans. The Immune Tolerance Network is specifically focused on studies to delineate the mechanisms of immune tolerance after transplantation and means of achieving tolerance in patients. (0%)

B2b. Develop new therapies for hepatitis C that are effective in the transplant situation. Several HCV-specific protease and polymerase inhibitors have been

developed and are in phase I/II trials in patients with uncomplicated hepatitis C, but none have been evaluated in transplant patients. (0%)

B3a. Elucidate the pathogenesis of post-transplant lymphoproliferative disease (PTLD) and means of prediction, prevention, and control. The NIH-funded SPLIT study group is currently addressing the issue of post-transplant complications and morbidities, including the issue of PTLD and focusing on potentially modifiable risk factors. Low dose chemotherapy is effective in at least two-thirds of cases (Gross TG. *J Clin Oncol* 2005;23:6481). (10%)

B3b. Develop means of improving regeneration after living donor liver transplantation. Regeneration of the liver after live donor liver transplantation is important for both recipient and donor. In animal models, infusions of IL-6 and pretreatment with thyroid hormone improve regeneration; studies in humans have not been done. (0%)

C1a. Define factors important in long-term success of liver transplantation in children as defined by quality of life and social/psychological development. The SPLIT study group is currently accumulating data on factors associated with long-term successful liver transplantation in children, including functional outcomes in terms of quality of life and academic achievement. (0%).

C1b. Determine efficacy of chemotherapy and local ablative treatment of HCC done in the peri-transplant period. The recently released program announcement entitled, "Etiology, Prevention, and Treatment of Hepatocellular Carcinoma" (PA-05-137) encourages research in local ablative therapy. (0%)

C2a. Based upon molecular mechanisms, develop and assess tolerance-inducing regimens, including studies in children. Trials of new agents or combinations of agents that might accelerate tolerance have been proposed in the SPLIT study group. (0%)

C2b. Identify biomarkers that predict tolerance and the ability to discontinue immunosuppression after liver transplantation. The NIH-sponsored Immune Tolerance Network serves as the umbrella organization of a trans-NIH effort to clinically characterize immunological tolerance in transplantation. (0%)

C3a. Develop means to prevent recurrence of hepatitis C after liver transplantation. Trials of peginterferon and ribavirin therapy in patients before transplantation aimed at prevention of recurrence are underway in the A2ALL cohort study. Small pilot studies of HCIG from Canada and from the NIH-funded Antiviral Cooperative Study Group (ACSG) demonstrated no effect of this product in preventing recurrence. (10%)

C3b. Develop gene or cell therapy for at least one metabolic liver disease that delays or replaces liver transplantation. The NIH research portfolio supports several R01 grants focused on gene and cell therapy of liver diseases that are currently treated with transplantation, including alpha-1-antitrypsin deficiency, PFIC, and Crigler-Najjar syndrome. Gene therapies are being evaluated in animal models, but not in human subjects with these diseases. (0%)

Figure 14. Estimated Progress on Liver Transplantation Research Goals, 2005 (Year 1)